

SESSION III

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A phase II study of prophylactic intravesical chemotherapy with 4'-epirubicin in recurrent superficial bladder cancer: comparison of 4'-epirubicin and Adriamycin

Abstract Since intravesical recurrence of superficial bladder cancer (Ta, T1) after transurethral resection (TUR) is frequent, adjuvant therapy to reduce the recurrence rate has been extensively investigated. Although intravesical chemotherapy has been employed for 30 years or more, neither the exact effect on the bladder epithelium nor the optimal dose and administration schedule has yet been clarified. In recent years, several derivatives of Adriamycin (ADR) have been developed, and 4'-epirubicin (FARM) is one of them. This drug has been shown to have antitumor effects almost equal to those of ADR and to produce less toxicity when given systemically as chemotherapy. In an attempt to clarify the effect of intravesical FARM in the prevention of recurrence of superficial bladder cancer, we conducted a

prospective randomized trial to compare the effects of equal doses of FARM and ADR given by intravesical instillation after TUR in cases of highly recurrent superficial bladder cancer. A total of 73 patients with recurrent superficial bladder cancer were randomized to receive TUR and either 30 mg FARM or 30 mg ADR by intravesical instillation every 2–4 weeks for 1 year. The prophylactic effect on recurrence and the toxic effects of these drugs were investigated. The current results show that FARM provides efficacy almost equal to that of ADR in the prevention of recurrence in these patients. However, FARM also caused almost the same local toxic effects (bladder irritation, among others) as ADR. On the basis of these preliminary results, FARM is surmised to be one of the agents as beneficial as ADR in the prevention of recurrence of superficial bladder cancer.

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Key words Intravesical chemotherapy · Superficial bladder cancer · 4'-Epirubicin

Abbreviations ADR Adriamycin · FARM Farmorubicin (4'-epirubicin)

Introduction

The recurrence of tumors after transurethral resection (TUR) is one of the major problems in the treatment of superficial bladder cancer [11, 12]. Implantation of tumor cells after surgical treatment as well as the multifocal nature of tumor development are major factors favoring tumor recurrence [12]. To reduce implantation of tumor cells after TUR, instillation of anticancer drugs has been advocated as an adjuvant therapy to destroy newly implanted cancer cells [2, 4]. Since 4'-epirubicin (FARM) has the same antitumor effect as Adriamycin (ADR) and is less toxic than ADR in systemic application [3, 5, 6], we anticipated that FARM might be a better agent than ADR for intravesical instillation therapy, as it is capable of exerting a good prophylactic

Recurrent superficial bladder cancer cases

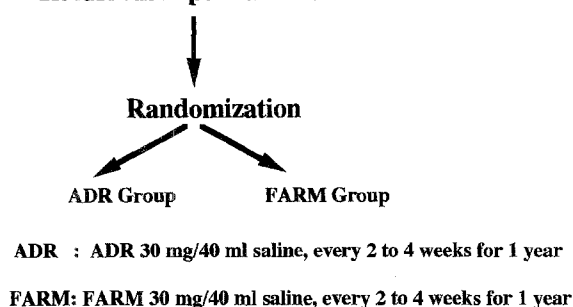


Fig. 1 Design of our protocol

Table 1 Participating institutions

Yokohama City University School of Medicine	M. Hosaka
Kanagawa Cancer Center Hospital	I. Kondo
Yokohama Municipal Hospital	S. Fukushima
Yokohama Minami Kyosai Hospital	H. Fukuoka
Yokohama Municipal Kowan Hospital	K. Miyai
Yokohama Senin Hoken Hospital	E. Sasaki
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Oguchi Higashi Sogo Hospital	M. Fukuda
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National Yokosuka Hospital	A. Furuhashi
Yokosuka Hokubu Kyosai Hospital	A. Kodaira
Kawasaki Municipal Ida Hospital	H. Shiozaki
Odawara Municipal Hospital	T. Yoshimura
Fujisawa Citizens' Hospital	M. Hirokawa
Yamato Municipal Hospital	H. Kumagai
Chigasaki Municipal Hospital	T. Takeda
Kanagawa Prefectural Ashigara Hospital	M. Nakahashi
Hatano Red Cross Hospital	K. Saito
Shakaihoken Sagamino Hospital	K. Sato
National Atami Hospital	T. Ida
Hamaoka Municipal Hospital	N. Kitajima
Serioka Kokusai Hospital	S. Okamoto

effect on tumor recurrence and causes fewer local side effects.

We performed a prospective randomized chemotherapy trial of intravesical instillation of ADR and of FARM in equal doses into patients with highly recurrent superficial bladder cancers, in other words, a high-risk group for tumor recurrence. We compared the prophylactic effects of ADR and FARM on tumor recurrence as well as their toxicity.

Table 2 Characteristics of patients (NS, Not significant)

Characteristic	ADR group	FARM group	Total	χ^2 test
Sex:				
M	27	26	53	NS
F	6	6	12	
Age (years):				
<40	1	2	3	NS
40–49	3	1	4	
50–59	8	3	11	
60–69	7	8	15	
≥ 70	14	18	32	
Previous treatment ^a :				
No	12	10	32	NS
Yes	21	22	33	

^a Previous intravesical chemotherapy

Patients entered in this study

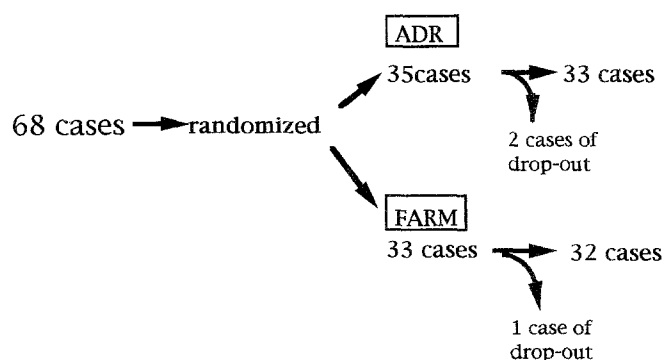


Fig. 2 Patients entered in this study

Patients and methods

Patients

A total of 68 patients with recurrent superficial bladder cancer of stage Ta–T2 and grade 1–2 were entered into this trial from April 1990 to December 1993 at Yokohama City University Hospital and its affiliated hospitals (Fig. 1, Table 1). Before TUR, these patients were randomized to 35 cases in an ADR group ($n = 35$) and a FARM group ($n = 33$, Fig. 2).

Treatment schedule

Bladder instillation was performed using 30 mg ADR or FARM in 40 ml saline. The drug solution was retained in the bladder for at least 2 h. This instillation was performed every 2 weeks for the first 3 months after TUR and then every 4 weeks for 1 year (Fig. 1).

Results

Background factors of patients

The patients' background factors, such as age, previous treatment before entrance in this study, and the number of tumor recurrences experienced before this study, were almost the same in the ADR and FARM groups (Table 2).

Table 3 Tumor size, number, site, grade, and stage at TUR

Characteristic	ADR group	FARM group	Total	χ^2 test
Size:				
1 cm	27	26	53	NS
1–3 cm	6	4	10	
3–5 cm	0	2	2	
>5 cm	0	0	0	
Number:				
1	9	19	18	
2–4	18	11	29	
≥ 5	6	5	11	
Grade:				
G1	13	16	29	NS
G2	20	19	39	
Stage:				
Ta	21	22	43	NS
T1	9	8	16	
Unknown	3	2	5	
Site:				
Urethra	0	0	0	
Neck	6	4	10	
Trigone	8	7	15	
Posterior wall	16	14	30	
Lateral wall	16	11	27	
Apex	4	2	6	
Anterior wall	6	4	10	
Unknown	0	1	1	

The tumor size and number were almost the same in the ADR and FARM groups. The grades and stages of the tumors in both groups showed no statistically significant difference (Table 3). Nearly half of the patients entered in this study had highly recurrent disease (Table 4).

Tumor recurrence rate

We compared the incidences of tumor recurrence between the ADR and FARM groups. In all, 9 of 33 patients (27%) in the ADR group and 8 of 32 patients (25%) in the FARM

group experienced tumor recurrence during or after the instillation therapy (Table 5). Thus, the rate of tumor recurrence did not differ between the two groups. Next, the tumor-free period after TUR was compared between the ADR and FARM groups. The tumor-free period ranged from 3 to 16 months in the ADR group and from 4 to 17 months in the FARM group (Table 5). The mean tumor-free period was 8.5 months in the ADR group and 9.7 months in the FARM group (Table 5). There was no significant difference in the tumor-free period between the two groups. Table 6 shows the data on the grade and stage of the recurrent tumors after this therapy.

Table 4 Number of tumor recurrences before entry into this study

Number of recurrences	ADR group	FARM group	χ^2 test
–	14	18	NS
1	8	4	
2	5	4	
3	0	4	
4	3	0	
5	0	0	
6	3	2	

Table 5 Recurrent cases and tumor-free period

Group	Number of recurrent cases (%)	Tumor-free period after TUR	Mean
ADR	9 (27%) ^a	3–16 months	8.5 months
FARM	8 (25%) ^a	4–17 months	9.7 months

^a Not statistically significant in the X² test

Table 6 Characteristics of recurrent tumors after intravesical ADR or FARM

	ADR group	FARM group	χ^2 test
Site:			
Urethra	0	1	
Neck	2	0	
Trigone	1	3	
Posterior wall	6	5	
Lateral wall	4	2	
Apex	2	1	
Anterior wall	1	1	
Grade:			
G1	4	7	NS
G2	5	2	
G3	0	0	
Stage:			
Ta	6	5	NS
T1	3	2	
T2	0	0	
T3	0	0	

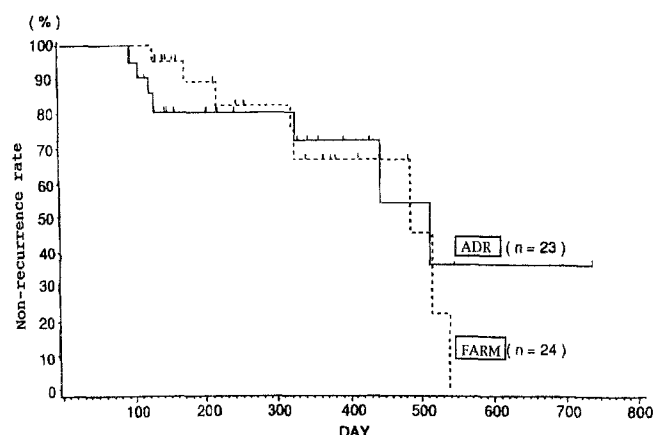


Fig. 3 Tumor nonrecurrence rates determined in the ADR and FARM groups. Log-rank, N.S.; Wilcoxon, N.S.

Figure 3 plots the tumor nonrecurrence rates for the ADR and FARM groups. Since this is a preliminary report, one-third of both groups of patients were compared. At present, there is no statistically significant difference in the tumor-free period between the ADR and FARM groups. There has been no case of grade G3 or invasive cancer in either group. Table 6 summarizes the sites of recurrent tumors. There has been no difference in the sites of recurrence between the two groups.

Toxicity

One of the reasons for this clinical study was the hope that FARM might cause a lower incidence of local side effects than does ADR. In the ADR group ($n = 33$ cases), there were 2 cases each of pollakisuria, pain on urination, and hematuria. In all, 5 (15%), 5 (15%), and 4 (12%) of the 32 patients in the FARM group complained of pollakisuria, pain on urination, and hematuria. There has been no statistically significant difference in the incidence of these local side effects between the ADR and FARM groups (Table 4).

Discussion

Although superficial bladder cancers usually have a good prognosis, they are troublesome because of the high incidence of tumor recurrence after TUR. It is well recognized that postoperative intravesical chemotherapy is

effective in preventing tumor recurrence [9, 10]. For that reason, several anticancer agents have been used as post-operative intravesical chemotherapy to prevent tumor recurrence [2, 4]. However, some questions remain concerning the timing of instillation, the duration of the instillation period, and the choice of drugs [7, 8, 13]. Another problem in this therapy is the relatively high incidence of local toxic effects such as hematuria, pain on urination, and pollakisuria [9]. Because of such toxicity, bladder instillation therapy is often discontinued or interrupted.

In this preliminary study, we conducted prophylactic intravesical chemotherapy with FARM after TUR, expecting an equal, if not better prophylactic effect on tumor recurrence and lower local toxicity than that produced by ADR. We showed that the tumor nonrecurrence rate observed in the FARM group was almost the same as that seen in the ADR group (Fig. 3). Although a progression in the histological grade of superficial tumors has been reported with long-term intravesical chemotherapy [1], our study had no such case. Thus, FARM is as effective and reliable as ADR in intravesical chemotherapy for the prevention of bladder-tumor recurrence. Although we expected that FARM might produce less local toxicity than ADR, the incidence of local toxic effects observed in the FARM group was also equal to that seen in the ADR group. We speculate that the concentration of both drugs in bladder instillation therapy is so high that there is no difference in the incidence of local toxic effects with FARM instillation therapy. It is also noteworthy that there has been no case of systemic side effects.

In summary, a randomized trial of bladder instillation therapy using equal doses of FARM and ADR was performed in highly recurrent cases of superficial bladder cancer. Although our results are preliminary, intravesical FARM showed efficacy in the prevention of recurrence almost equal to that obtained with the same dose of ADR. FARM produced local toxic effects on the bladder that were similar to those caused by ADR. FARM should be regarded as one of the agents as reliable as ADR in intravesical chemotherapy.

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Table 7 Toxicity encountered with intravesical ADR or FARM

Side effect (moderate to severe)	ADR (33 patients)	FARM (32 patients)	χ^2 test
Pollakisuria	2	5	NS
Pain on urination	2	5	NS
Hematuria	2	4	NS

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